Systematic Review and Meta-Analysis

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Laparoscopic versus open nephroureterectomy for upper urinary tract urothelial carcinoma

A systematic review and meta-analysis

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Abstract

Purpose: To evaluate the efficacy and safety of laparoscopic nephroureterectomy (LNU) and open nephroureterectomy (ONU) for the treatment of upper urinary tract urothelial carcinoma (UTUC).

Methods: PubMed, Embase, and Cochrane databases were selected for systematic review of trials that compared outcomes of LNU and ONU. Meta-analysis was performed using RevMan 5.3 and STATA 13.0 software.

Results: LNU was associated with longer operation time ($P < .001$), shorter hospital stay ($P < .001$), less blood loss ($P = .006$) and lower rate of transfusion ($P < .001$). The occurrence of complications, including minor ($P = .52$), major ($P = .21$) and total complications ($P = .19$) were similar between LNU and ONU. There was no significant difference in the rate of 5-year recurrence-free survival ($P = .90$), 5-year cancer-specific survival ($P = .12$), and 5-year overall survival ($P = .11$) as well as 2-year RFS ($P = .84$), 2-year CSS ($P = .86$), and 2-year OS ($P = .25$).

Conclusion: Our results indicated that LNU is a safe and effective method to treat UTUC. Given the limitations of this study, further multicenter, randomized trials are required to confirm these findings.

Abbreviations: CIs = confidence intervals, CSS = cancer-specific survival, FE = fixed-effects, LNU = laparoscopic nephroureterectomy, ONU = open nephroureterectomy, OR = odds ratio, OS = overall survival, RE = random-effects, RFS = recurrence-free survival, RR = risk ratio, UTUC = urinary tract urothelial carcinoma, WMD = weighted mean difference.

Keywords: laparoscopic nephroureterectomy, meta-analysis, open nephroureterectomy, urinary tract urothelial carcinoma

1. Introduction

Urothelial carcinoma of the upper urinary tract (UTUC) is a type of rare malignancy accounting for 1% to 5% of all urological tumors.[1] Due to its characteristics of rapid progression, tissue invasion and body deterioration, radical nephroureterectomy with bladder cuff excision is the standard treatment for UTUC, especially for muscle-invasive and/or high-grade disease.[2]

Currently, open nephroureterectomy (ONU) is the most commonly performed procedure for high-risk UTUC. Although ONU has been proven to provide long-term local control and improve survival, it may be associated with significant morbidity.[2] Since the first laparoscopic nephroureterectomy (LNU) was performed in 1991, minimally invasive approaches have rapidly evolved, and laparoscopic surgery of the upper urinary tract has become increasingly accepted by the urological community.[3] LNU is considered to be equally effective as ONU surgery for UTUC, while resulting in less perioperative morbidity. However, UTUC is biologically aggressive malignancy with a high potential for disease recurrence and eventual death. It is hypothesized that tumor dissection and high-pressure pneumoperitoneum during LNU are associated with a higher risk of bladder or local recurrence as well as port-site metastasis.[4] Hence, the oncologic efficacy of LNU versus ONU remains controversial.

Several studies have compared the outcomes of LNU and ONU for selected cases of UTUC. Nevertheless, the role of LNU is not yet established. Although a meta-analysis comparing LNU and ONU was published in 2012,[5] the surgical technique and experience have vastly developed since then. Hence, we conducted this meta-analysis based on trials published in the past 10 years, to evaluate the advantages and disadvantages of LNU for the surgical treatment of UTUC in terms of perioperative, postoperative and survival parameters.

2. Materials and methods

The present meta-analysis was conducted based on the recommendations of the PRISMA guidelines. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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2.1. Study selection

A systematic search of PubMed, Embase, and Cochrane online databases was performed to identify all studies published in the past 10 years (2007–2017), which compared LNU with ONU using the following MESH search headings: "comparative studies," "laparoscopic," "open," "radical nephroureterectomy," and "urothelial carcinoma of the upper urinary tract." The "related articles" function was used to broaden the search, and all abstracts, studies, and citations were reviewed. Additionally, the reference lists of selected articles were manually reviewed to identify other potentially relevant articles.

2.2. Inclusion and exclusion criteria

The included trials met the following requirements: studies comparing LNU with ONU, patients with urothelial carcinoma of the upper urinary tract, reports on at least one outcome of interest mentioned below such as operation time, hospital stay, estimated blood loss, blood transfusion, complications, 5-year and/or 2-year survival and the relative data were reported or could be calculated, and published in the last 10 years (2007–2017).

Studies were excluded if the inclusion criteria were not met, no outcomes of interest were reported or it was impossible to calculate or extrapolate the necessary data from the published results, children were included in the studies, and published before 2006.

2.3. Data extraction and outcomes of interest

Two reviewers independently extracted the following data: first author, year of publication, country, study interval, study design, number of patients who underwent LNU or ONU, mean age of the patients, ratio of males and females and length of follow-ups. The study qualities were assessed using the Newcastle–Ottawa scale (NOS).[6] Pathological stage and grade of tumor were also collected.

The following outcomes were extracted to compare LNU and ONU. Perioperative variables including operation time, length of hospital stay, and blood transfusion rate. Postoperative complications including minor complications (Clavien grades 1 and 2), and major complications (Clavien grades 3–5). The oncological outcomes including 2-year and 5-year recurrence-free survival (RFS), 2-year and 5-year cancer-specific survival (CSS), and 2-year and 5-year overall survival (OS).

In all cases of missing or incomplete data, the corresponding authors were contacted, but no additional information was provided. If no response was received, the methods introduced by Tierney were used to calculate or estimate the useful data from other information, such as the Kaplan–Meier curves.[7] All disagreements about eligibility were resolved by a third author through discussion until a consensus was reached.

2.4. Statistical analysis

The weighted mean difference (WMD) was used for continuous variables, the odds ratio (OR) was used for dichotomous parameters and the risk ratio (RR) for survival parameters, all with 95% confidence intervals (CIs). For studies presenting continuous data as means and range, we made an approximate transformation using the technique described by Hozo et al.[8] All pooled effects were determined by the z test and $P < .05$ was considered statistically significant. The heterogeneity of the treatment effects among included trials was evaluated using Q statistic and I^2 statistic. When $I^2 < 50\%$, $P > .1$, the evidences showed no significant heterogeneity, we used fixed-effects (FE) model, otherwise we used random-effects (RE) model. Sensitivity analyses were performed by omitting one study at a time. All the statistical analyses were performed using RevMan 5.3 (Cochrane Library Software, Oxford, UK). Egger's test and Begg's test were used to assess publication bias. All reported P values were 2-sided and $P < .05$ was regarded as significant for all included trials. The trim-and-fill method was also used to overcome the publication bias.[9] This process was done by STATA (Version 13.0; Stata Corp, Texas).

3. Results

3.1. Characteristics of selected studies

A total of 394 records were retrieved through database search. After screening, 25 trials[10–35] were selected for our meta-analysis (Fig. 1), which included 3489 patients who underwent LNU and 5732 patients who underwent ONU. The NOS of included studies ranged from 5 to 8. The characteristics of these studies are shown in Table 1. The pathological stages and grades

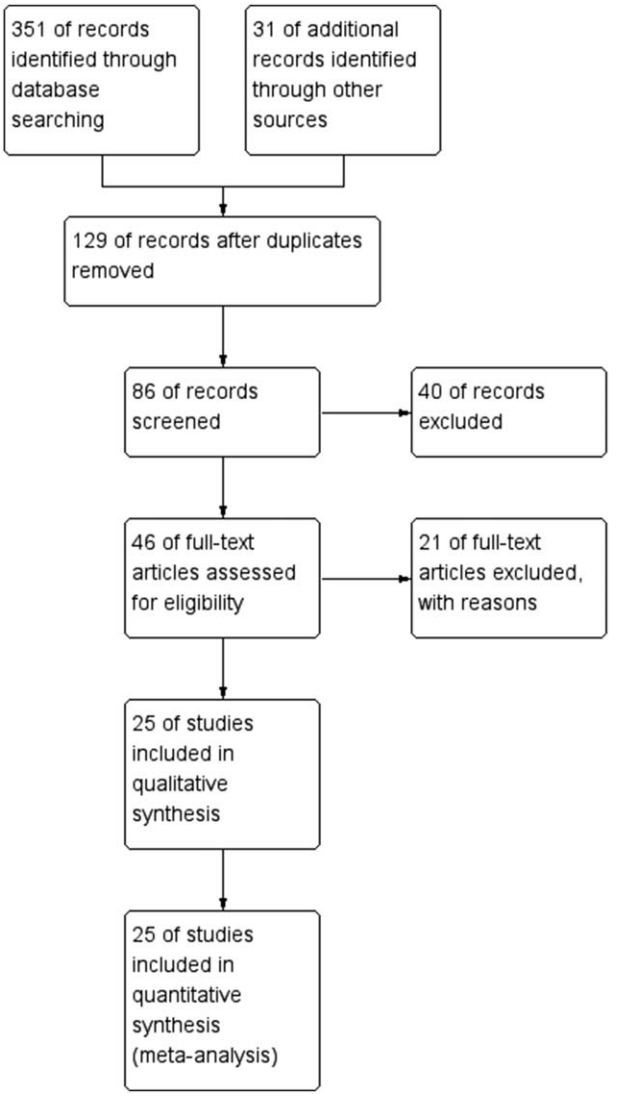

Figure 1. Flowchart showing the study selection process for meta-analysis.

Table 1

Characteristics of the included studies.

First author, year	Country	Study interval	Study type	Age mean (range)	Gender, Male/Female	No. of patients, LNU/ONU	Follow-up/months mean (range)	NOS
Ariane 2012	France	1995–2010	Retrospective	69.8 (61.9–76)	415/194	150/459	27 (10–48)	6
Blackmur, 2015	UK	1992–2010	Retrospective	67.8 (57.1–77.3)	14/12	13/13	2.8–187	6
Capitanio, 2009	Multi Institutional	1987–2007	Retrospective	68.7 (27–97)	846/403	270/979	60	8
Fairey, 2013	Multi Institutional	1994–2009	Retrospective	71.5	542/307	446/403	26.4 (7.2–60)	7
Favaretto, 2010	USA	2002–2008	Retrospective	71.7 (64–78)	NA	53/109	60	6
Fradet, 2014	Canada	1990–2010	Retrospective	67 (59–75)	NA	345/267	40.4 (7.7–56.8)	7
Greco, 2009	Germany	1999–2003	Retrospective	66.8	76/64	70/70	60	7
Hanske, 2015	Multi Institutional	2006–2012	Retrospective	70.3	573/323	599/297	1	6
Hemal, 2008	India	1998–2006	Retrospective	55.9	27/21	21/27	55.3 (3–79)	6
Kim, 2015	Korea	1992–2012	Retrospective	64.7 (57.7–70.8)	287/84	100/271	50.8 (26.6–103.6)	8
Kitamura, 2014	Japan	1995–2010	Retrospective	68.3 (32–88)	NA	65/34	60 (6–192)	6
Koda, 2007	Japan	1995–2005	Retrospective	70.4	80/26	79/27	17.5 (1–97)	8
Liu, 2017	China	2000–2013	Retrospective	62	198/67	52/213	60	8
Manabe, 2007	Japan	2000–2004	Retrospective	72 (48–84)	154/70	58/166	13.6–28	6
Metcalfe, 2012	Canada	1994–2009	Retrospective	69.7	653/375	446/403	60	5
Miyazaki, 2016	Japan	2005–2011	Retrospective	69.7	504/245	222/527	39 (0.1–79.3)	6
Rouprêt, 2007	France	1994–2004	Retrospective	70	34/12	20/26	24	7
Simone, 2009	Italy	2003–2006	RCT	60.45	50/30	40/40	41 (30–66)	8
Stewart, 2011	UK	1992–2000	Retrospective	67.8	33/29	23/39	163	7
Taweemonkongsap, 2008	Thailand	2001–2007	Retrospective	65.25	33/27	31/29	27.1 (3–72)	7
Terakawa, 2008	Japan	2000–2005	Retrospective	70	NA	120/120	29.5	7
Waldert, 2008	Austria	1999–2006	Retrospective	67.2	61/31	43/59	41	7
Walton, 2010	Multi Institutional	1987–2008	Retrospective	68 (61–75)	533/240	70/703	34 (15–65)	7
Xylinas, 2013	France	1995–2009	Retrospective	67.7 (60–76)	332/150	132/350	39.5 (25–60)	5
Zou, 2014	China	1999–2013	Retrospective	63.7 (35–80)	87/35	21/101	53 (3–159)	6

LNU = laparoscopic nephroureterectomy, NA = not applicable, NOS = Newcastle–Ottawa Scale, ONU = open nephroureterectomy, RCT = randomized controlled trial.

(if available) of involved patients from the trials are shown in Tables 2 and 3.

3.2. Outcomes of perioperative variables

The LNU group was associated with longer operation time/min (WMD: 44.85; 95% CI: 24.89 to 64.80; $P < .001$). The hospital stay was significantly shorter in the LNU group (WMD: −2.46; 95% CI: −3.12 to −1.80; $P < .001$) as compared to the ONU group. Besides, LNU resulted in less estimated blood loss (WMD: −137.83; 95% CI: −236.77 to −38.89; $P = .006$) and consequently lower rate of blood transfusion (OR: 0.43; 95% CI: 0.31 to 0.60; $P < .001$). These perioperative outcomes are shown in Figure 2.

Table 2

Pathological stages of the patients in the included trials.

First author, year	Ta, Tis (LNU/ONU)	T1 (LNU/ONU)	T2 (LNU/ONU)	T3 (LNU/ONU)	T4 (LNU/ONU)
Ariane, 2012	44/119	31/113	20/45	53/153	2/29
Blackmur, 2015	10/10	0/0	1/1	2/2	0/0
Capitanio, 2009	103/204	69/229	35/202	59/306	4/38
Fairey, 2013	NA	NA	66/66	99/89	21/22
Greco, 2009	13/14	17/16	39/37	1/3	0/0
Hemal, 2008	3/4	8/9	8/11	2/3	0/0
Kitamura, 2014	3/16	7/10	8/11	16/28	0/0
Koda, 2007	17/8	20/6	11/6	28/7	3/0
Liu, 2017	0/0	20/65	10/46	NA	NA
Manabe, 2007	12/29	16/41	6/16	24/73	0/7
Miyazaki, 2016	0/0	0/0	58/154	154/329	10/44
Rouprêt, 2007	6/6	9/5	2/5	2/7	1/3
Simone, 2009	0/0	20/12	8/15	12/13	0/0
Stewart, 2011	10/20	7/8	3/2	3/9	0/0
Taweemonkongsap, 2008	0/0	16/13	10/12	4/4	1/0
Terakawa, 2008	34/24	25/26	19/27	40/43	2/0
Waldert, 2008	11/13	9/16	5/10	18/20	0/0
Walton, 2010	10/153	20/175	8/139	19/196	4/40
Zou, 2014	0/0	8/40	10/38	2/18	1/5

LNU = laparoscopic nephroureterectomy, NA = not applicable, ONU = open nephroureterectomy.

3.3. Outcomes of complications

We pooled data on complications from the included studies. The results showed no significant differences between LNU and ONU in minor (OR: 1.17; 95% CI: 0.73 to 1.88; $P = .52$), major (OR: 0.63; 95% CI: 0.31 to 1.29; $P = .21$) and total complications (OR:

Table 3

Pathological grades of the patients in the included trials.

First author, year	G1 (LNU/ONU)	G2 (LNU/ONU)	G3 (LNU/ONU)
Ariane, 2012	11/39	41/166	98/254
Blackmur, 2015	1/1	9/9	3/3
Greco, 2009	15/17	47/45	8/8
Hemal, 2008	6/8	11/13	4/6
Kitamura, 2014	1/2	14/33	19/30
Koda, 2007	10/3	33/16	36/8
Manabe, 2007	4/15	31/87	23/64
Miyazaki, 2016	4/8	72/189	146/324
Simone, 2009	6/5	22/22	12/13
Stewart, 2011	3/4	7/20	13/15
Terakawa, 2008	8/15	69/57	43/48
Waldert, 2008	6/4	19/31	18/24
Walton, 2010	11/88	5/219	54/396

LNU = laparoscopic nephroureterectomy, ONU = open nephroureterectomy.

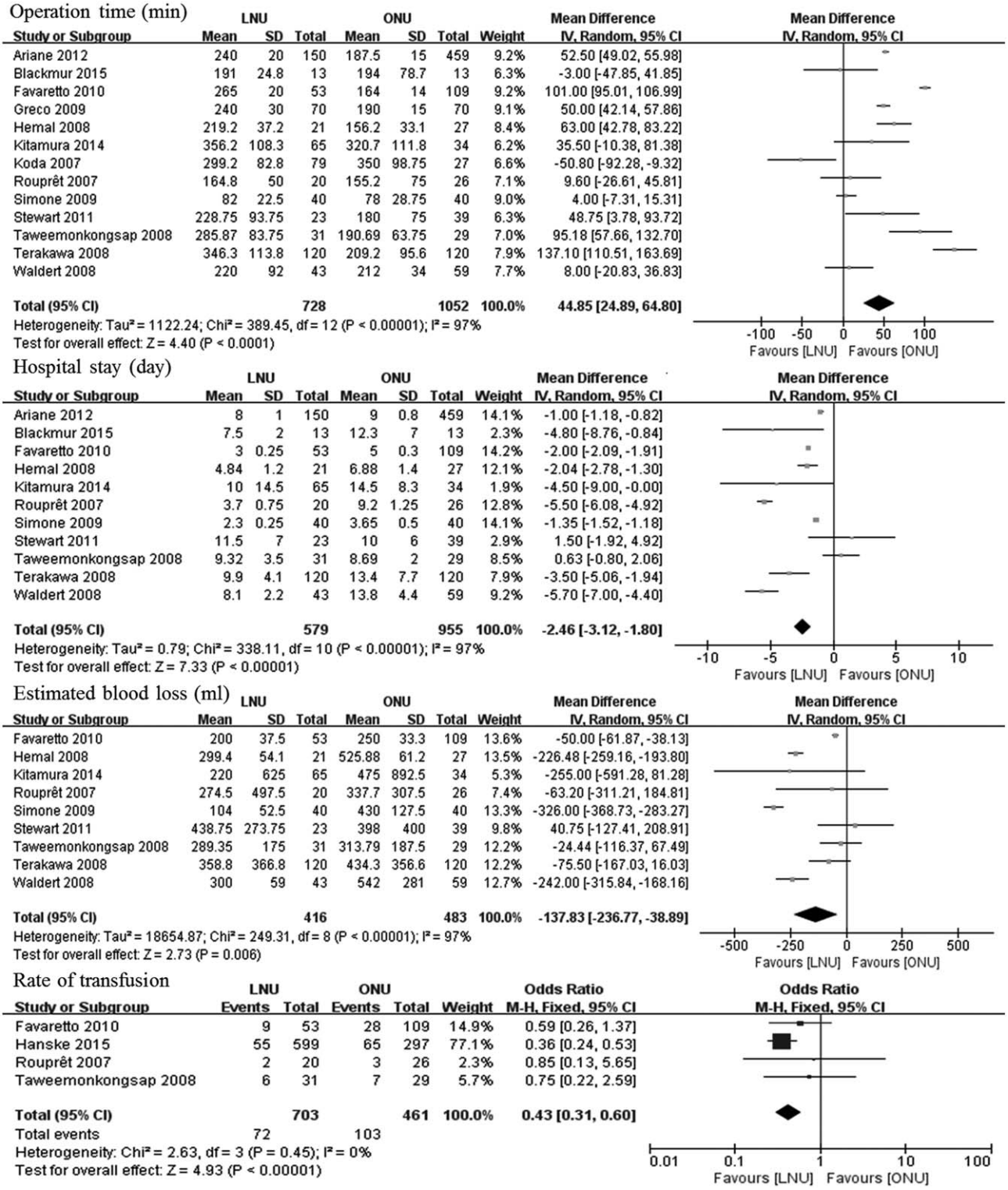

Figure 2. Forest plot and meta-analysis of perioperative parameters.

1.22; 95% CI: 0.91 to 1.65; $P=.19$). The data are shown in Figure 3.

3.4. Outcomes of survival

Survival variables were compared between LNU and ONU. The rate of 5-year RFS (RR: 1.01; 95% CI: 0.92 to 1.10; $P=.90$), 5-year CSS (RR: 1.04; 95% CI: 0.99 to 1.10; $P=.12$), and 5-year OS (RR: 1.08; 95% CI: 0.98 to 1.18; $P=.11$) as well as 2-year RFS (RR: 0.99; 95% CI: 0.87 to 1.12; $P=.84$), 2-year CSS (RR: 1.01; 95% CI: 0.94 to 1.07; $P=.86$) and 2-year OS (RR: 1.04; 95% CI: 0.97 to 1.12; $P=.25$) were similar between the LNU group and ONU group. The survival comparisons are shown in Figure 4.

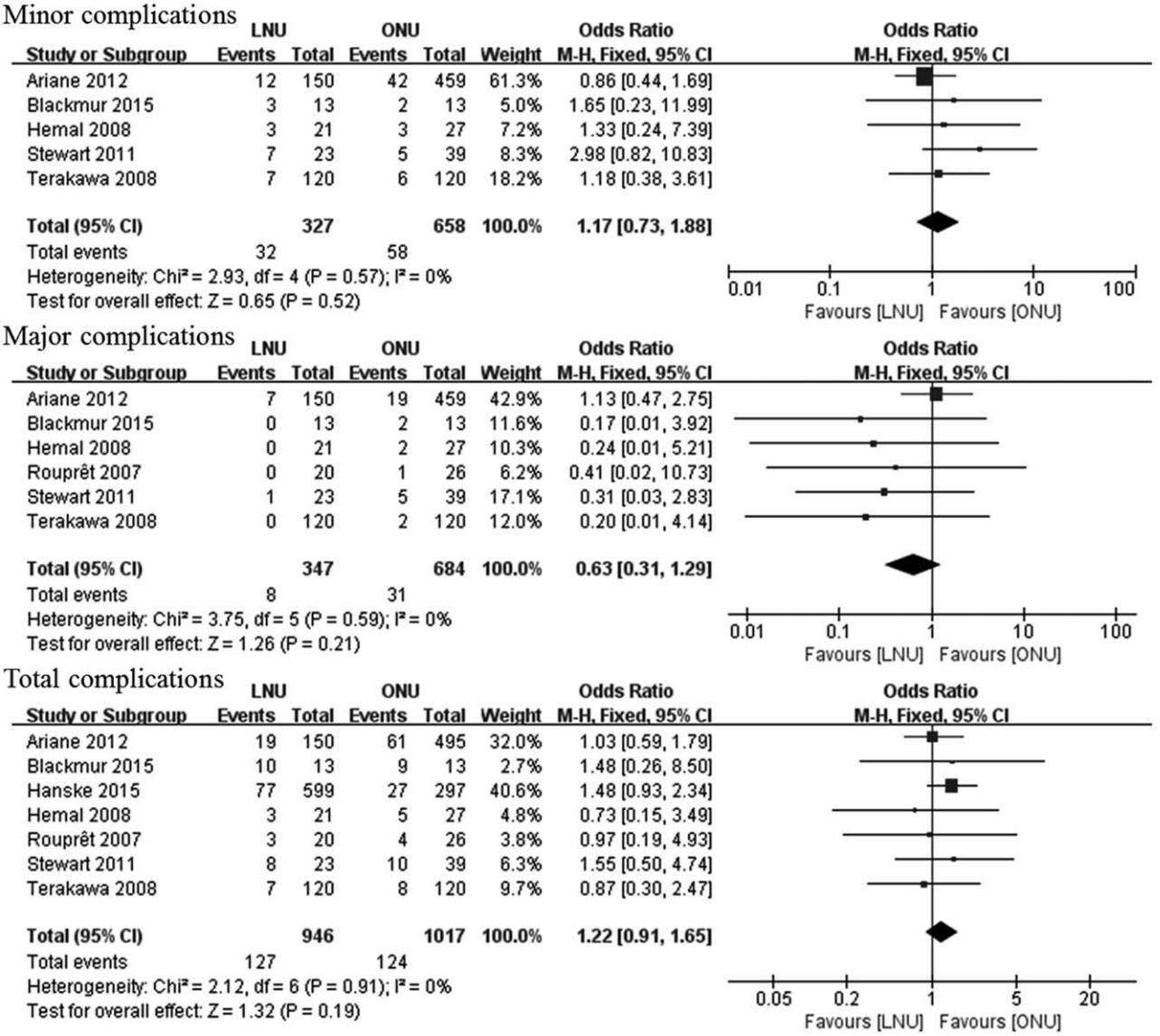

Figure 3. Forest plot and meta-analysis of complications.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing one study at a time. The significance of the pooled comparison between the 2 groups was not influenced by removing any single study, indicating that the results of our meta-analysis were stable. Egger's test and Begg's test were used to assess the publication bias of the included studies. The results are shown in Table 4. Although Begg's test showed no evidence of publication bias for 5-year CSS, Egger's test showed potential evidence of publication bias ($P = .044$). However, the results were not influenced after adjustment for publication bias using the trim-and-fill method.

4. Discussion

Since the first report comparing LNU to ONU were published in 1993,[36] numerous trials have attempted to prove LNU as a feasible alternative of ONU for UTUC, but there is a lack of comprehensive comparison. Our present meta-analysis provided high-level evidence to establish the role of LNU in the surgical treatment of UTUC. The results demonstrated that LNU was associated with longer operation time ($P < .001$), shorter hospital stay ($P < .001$), less blood loss ($P = .006$), and lower rate of transfusion ($P < .001$). The complication and survival parameters of LNU were comparable with ONU.

The process of LNU consists of nephrectomy and distal ureterectomy, with the same oncological principle as ONU. Laparoscopic access can be conducted via transperitoneal or retroperitoneal spaces. Transperitoneal access provides more working space and easier manipulation, while retroperitoneal approach avoids disruption of the intraperitoneal organs and risk of intraperitoneal contamination by malignant cells.[37] The procedure of LNU has not yet been standardized, especially management of the distal ureter remains controversial. Various disposal methods have been described in the trials included in our meta-analysis, including open surgery,[26,31] the Pluck technique,[10,32] and the LigaSure Atlas system.[27] Open surgery

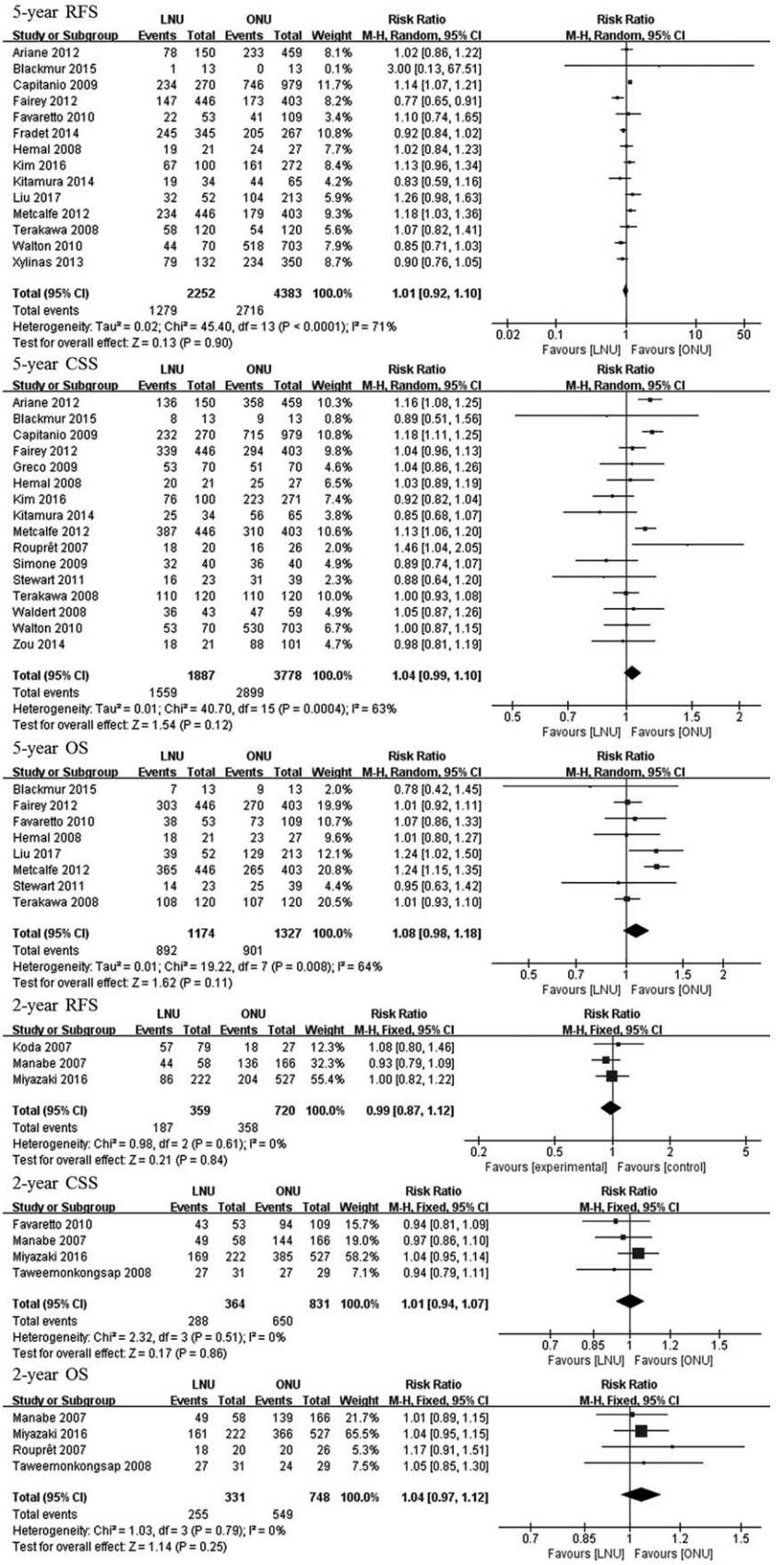

Figure 4. Forest plot and meta-analysis of survival. CSS = cancer-specific survival, OS = overall survival, RFS = recurrence-free survival.

Table 4

Egger's test and Begg's test results.

Outcome of interest	Number of included trials	*P* value of Egger's test	*P* value of Begg's test
Operation time	13	.566	.903
Hospital stay	11	.563	.938
Estimated blood loss	9	.283	.677
Complication	7	.405	.652
5-year RFS	14	.253	.903
5-year CSS	16	.044	.471
5-year OS	8	.565	.621

CSS = cancer-specific survival, OS = overall survival. Egger's test and Begg's test are not applicable when the included trials are < 5, RFS = recurrence-free survival.

remains most popular for bladder cuff excision. Nonetheless, no significant difference in oncological outcomes was reported among different techniques.[38] Subgroup analysis could not be performed based on different procedures due to insufficient data.

As a mini-invasive procedure, LNU has been accepted worldwide as a promising option, with certain advantages over ONU in terms of less blood loss, less requirement of transfusion, shorter hospital stay and lower financial cost.[39] But interestingly, in our meta-analysis, there was no significant difference in the occurrence of complications, including minor complications with Clavien grades 1 to 2 and major complications with Clavien grades 3 to 5. This is probably because enlarged incisions are necessary even in LNU for the removal of detached specimens as well as bladder cuff.

Previously, invasive or large tumors were contraindications for LNU.[2] Given the improvement of techniques and surgeons' experience, the criteria of LNU have been dramatically expanded. In our meta-analysis, patients with high stages (T3/T4) and high grades (G3) also underwent LNU, resulting in similar oncological outcomes as ONU. Despite different techniques, the oncological principles of surgical treatment of UTUC are the same. However, the high risk of regional recurrence and port-site metastasis in LNU remains concerning. Kondo et al[40] determinate that template-based lymphadenectomy reduces the risk of regional lymph node recurrence among patients with upper/middle ureteral cancer, however, templated lymphadenectomy is difficult for laparoscopic approach.

Xylinas et al[41] indicated that laparoscopic approach was an independent risk factor of intravesical recurrence, because high pressure might trigger tumor dissemination. Ariane et al[10] reported a significant number of port-side seeding cases in the LNU group. In contrast, other studies suggested that surgical modalities did not influence the postoperative recurrence or survival.[42–44]

Two meta-analyses have previously compared LNU and ONU, whereby LNU showed improvement in CSS and extravesical recurrence-free survival.[5,45] Nevertheless, based on the trials published in the last 10 years, either the 5-year survival or the 2-year survival variables did not differ between LNU and ONU. Moreover, we also focused on the perioperative parameters such as operation time, hospital stay and blood loss.

Our meta-analysis had some inherent limitations. First, only studies published in English were pooled in our analysis. Hence, relevant studies published in other languages might have been missed. Second, although Begg's and Egger's tests were performed, the influence of bias in this study could not be completely excluded. Third, the pathological variables, the length of follow-up, the operation procedures and the surgeons' experience were not the same in the trials, and the influence of heterogeneity could not be evaluated. Last, only one of the 25 trials included in our meta-analysis was an RCT, which lowered the strength of this meta-analysis.

A meta-analysis of comparative trials published in the last 10 years was performed to evaluate the efficacy and safety of LNU in the treatment of UTUC. The results revealed that LNU was a feasible alternative to ONU with similar oncological outcomes. Further multicenter RCTs with large sample size and high quality are required, including detailed data of patients' clinical characteristics, standard surgery procedures and fixed assessment point after operations.

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